UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,497	02/24/2004	Mark W. Becker	249.P2	9922

25000 7590 07/28/2009

GILEAD SCIENCES INC
333 LAKESIDE DR
FOSTER CITY, CA 94404

EXAMINER	
MARTIN, PAUL C	

ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
07/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/785,497	BECKER ET AL.	
	Examiner	Art Unit	
	PAUL C. MARTIN	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/8/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4-13, 15 and 16 are pending in this application and were examined on their merits.

The rejection of pending Claims 1, 4-13 and 15 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn due to the Applicant's amendments to the Claims filed 06/08/09.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Pending Claims 1, 4-7 and 11-13 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Cook *et al.* (1995) for reasons of record set forth below, slightly altered to take into account Applicant's amendments to the Claims filed 06/08/09.

Shaw *et al.* teaches a screening method comprising the steps of; providing a plurality of amino acid phosphonoester prodrugs of PMPA (Pg. 1825, Table 1), selecting two tissues (liver and intestine), administering the prodrug to both and determining the relative *in vitro* biological stability and bioavailability of PMPA in the samples (Pg. 1827, Column 1, Lines 7-8 and Column 2, Lines 1-14 and Table 3, and Pg. 1828, Column 1, Lines 1-10).

Shaw *et al.* teaches wherein the prodrug of PMEA was shown to significantly increase the oral bioavailability of PMEA in HIV infected patients and wherein PMPA has selective and potent inhibitory activity *in vitro* against retroviruses and wherein IV PMPA has been shown to reduce viral load in HIV infected patients (Pg. 1824, Column 2, Lines 1-9 and 16-18).

It is inherent in the method of Shaw *et al.* that the screening method would determine the relative antiviral activity conferred by the PMPA prodrug in the samples because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues and bodily fluids would necessarily also provide a determination of the *relative* antiviral activity of the prodrug in those tissues and fluids even if no virus were present.

Shaw *et al.* does not teach a method wherein the target tissue is not small intestine; selecting at least one target tissue, which is known to be a site of viral latency or infection and at least one non-target tissue; or the selection of a desired prodrug based on its relative antiviral activity.

Cook *et al.* teaches a method wherein anti-HIV ester-prodrugs are administered to several different species and determining the biological stability and bioavailability of the prodrug in small intestine and liver fractions as well as whole blood, red blood cells and plasma (Pg. 1161, Figs 2-4). Cook *et al.* further teaches that ester-type drugs and prodrugs are hydrolyzed by esterase enzymes present in intestinal mucosa, tissues (e.g. liver, kidney, eye) and blood, and the pharmacological activity and toxicity of the esters are markedly affected by the degree of hydrolysis.

The reference states that esterase activities in tissues are known to vary between species and that the purpose of the study was to determine whether species differences in bioavailability is due to species differences in ester hydrolysis rate or absorption of the prodrug itself as well as to determine the site(s) of ester hydrolysis (liver, intestine, RBC, plasma) (Pg. 1158, Column 2, Lines 24-40).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Shaw *et al.* to select a target tissue and non-target tissue wherein the target tissue is not small intestine because while the claimed invention excludes the use of small intestine and therefore excludes the reference as prior art for purposes of anticipation, the reference is still valid for all its teachings with regard to the obviousness of the claimed invention. One of ordinary skill in the art at the time of the invention would have known that viral infection can be tissue specific (i.e., lymphoid tissue for HIV and hepatic tissue for Hepatitis-B), therefore it would have been obvious to look at the bioavailability (hydrolysis) and stability of a prodrug which has known antiviral activity in a target tissue of interest as a means of ascertaining whether prodrug is reaching the target tissue in an active form and in what amounts. Further, one of ordinary skill in the art would have selected a non-target tissue of interest as a means of determining the potential for side effects (toxicity) in non-target tissue or the misdirection of prodrug and active drug to the wrong tissue.

Cook *et al.* teaches that it was well known at the time of the invention to screen various tissues and bodily fluids of different species for prodrug hydrolysis and that variations were known among both the site and degree of hydrolysis among species. It would have been obvious to one of ordinary skill in the art to select the prodrug showing the best biological stability and bioavailability of prodrug derived PMPA in various tissues and bodily fluids, and would necessarily also provide the best *relative* antiviral activity of the prodrug in those tissues.

Therefore, this type of tissue screening was well known at the time of the invention and it would have been desirable and well-within the purview of one of ordinary skill in the art to substitute another tissue such as liver, kidney, eye, etc. in place of the target tissue small intestinal homogenate in order to screen for the site of prodrug hydrolysis as well as the optimum bioavailability and biostability of a prodrug in those other tissues within a species. One of ordinary skill in the art would have been motivated to make this modification because of the ability to screen for the site (target tissue) of prodrug enzymatic hydrolysis as well as the bioavailability and biostability of prodrugs in various non-target tissues in different animal models. There would have been a reasonable expectation of making this modification because Shaw *et al.* teaches the use of two tissues as well as blood and Cook *et al.* teaches that prodrug screening in multiple tissues and blood fractions was well known in the art at the time of the invention.

Response to Arguments

Applicant's arguments filed 06/08/09 have been fully considered but they are not persuasive.

The Applicant argues that neither the Shaw *et al.* or Cook *et al.* references teach or suggest determining the tissue specificity of their prodrugs followed by selecting a prodrug based on those results, i.e., that they are not concerned with prodrug screening but with prodrug characterization, more specifically intraspecies bioavailability (Remarks, Pg. 6, Lines 22-24 and Pg. 7, Lines 1-2).

This is not found to be persuasive for the following reasons, as discussed above, Shaw *et al.* teach a screening method comprising the steps of; providing a plurality of amino acid phosphonoester prodrugs of PMPA (Pg. 1825, Table 1); selecting two tissues (liver and intestine), administering the prodrug to both and determining the relative *in vitro* biological stability and bioavailability of PMPA in the sample. Shaw et *al.* further teaches wherein PMPA has selective and potent inhibitory activity *in vitro* against retroviruses and wherein IV PMPA has been shown to reduce viral load in HIV infected patients.

It is inherent in the method of Shaw *et al.* that the screening method would determine the relative antiviral activity conferred by the PMPA prodrug in the samples because PMPA is a known potent antiviral compound and the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues and bodily fluids would necessarily also provide a determination of the *relative* antiviral activity of the prodrug in those tissues and fluids even if no virus were present.

One of ordinary skill in the art at the time of the invention would have known that viral infection can be tissue specific (i.e., lymphoid tissue for HIV and hepatic tissue for Hepatitis-B), therefore it would have been obvious to look at the bioavailability (hydrolysis) and stability of a prodrug which has known antiviral activity in a target tissue of interest as a means of ascertaining whether prodrug is reaching the target tissue in an active form and in what amounts. Further, one of ordinary skill in the art would have selected a non-target tissue of interest as a means of determining the potential for side effects (toxicity) in non-target tissue or the misdirection of prodrug and active drug to the wrong tissue. It would have been obvious to one of ordinary skill in the art to select the prodrug showing the best biological stability and bioavailability of prodrug derived PMPA in various tissues and bodily fluids, and would necessarily also provide the best *relative* antiviral activity of the prodrug in those tissues.

The Applicant argues that the claimed invention was intended to exclude bioavailability studies, that determining the bioavailability of prodrugs involves administering a preselected prodrug to a test animal and then determining the distribution of the parental drug (hydrolysis product) as an indicia of prodrug absorption, that these studies lack the step of selecting from a plurality of prodrugs, and that they do not test a target tissue that is a site for viral latency or infection (Remarks, Pg. 7, Lines 3-11).

This is not found to be persuasive for the following reasons, whether or not Applicant intended to exclude bioavailability studies, the fact is the claimed invention has not distinguished itself from Prior Art references which are bioavailability studies. As discussed above, one of ordinary skill in the art at the time of the invention would have known that viral infection can be tissue specific (i.e., lymphoid tissue for HIV and hepatic tissue for Hepatitis-B), therefore it would have been obvious to look at the bioavailability (hydrolysis) and stability of a prodrug which has known antiviral activity in a target tissue of interest as a means of ascertaining whether prodrug is reaching the target tissue in an active form and in what amounts. Further, one of ordinary skill in the art would have selected a non-target tissue of interest as a means of determining the potential for side effects (toxicity) in non-target tissue or the misdirection of prodrug and active drug to the wrong tissue. Further, one of ordinary skill in the art would have recognized the obviousness of selecting the prodrug showing the best biological stability and bioavailability in target tissues and bodily fluids because this would necessarily also provide the best *relative* antiviral activity of the prodrug in those specific tissues.

Pending Claims 1, 4-7, 9-13, 15 and 16 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Shaw *et al.* (1997) in view of Cook *et al.* (1995) and further in view of Glazier *et al.* (US 5,627,165) for reasons of record set forth below, slightly altered to take into account Applicant's amendments to the Claims filed 06/08/09.

The teachings of Shaw *et al.* and Cook *et al.* were discussed above.

Glazier *et al.* teaches a method of screening for antiviral activity of a plurality of PMEA [9-(2-phosphonylmethoxyethyl)adenine] prodrugs on HIV infected human T-lymphocyte (target lymphatic tissue) (CEMss) and HBV infected hepatocytes (target liver tissue) and by administering the prodrug to a target tissue (HIV/HBV infected) and a non-target (uninfected) control lymphoid and hepatic tissue; and determining the antiviral activity conferred by the prodrug on the tissues and selecting a prodrug having an activity in the infected tissue greater than 10 times that if the non-infected tissue. (Column 36, Lines 35-48 and Column 37, Lines 5-22 and Columns 38 and 39, Tables).

Glazier *et al.* teaches wherein mice are administered with a dansyl phosphonate prodrug and the relative activity of the prodrug in blood, liver, spleen and kidney samples is determined wherein the levels of relative activity of the pro-drug are at least 10 times greater in the liver than in the spleen (Column 41, Lines 44-67 and Column 42, Lines 1-27 and Figs 7C and 9C).

Glazier *et al.* is not an anticipatory reference because it does not teach wherein the target and non-target tissues are not the same tissue, the test and control tissues are from the same cell line.

Neither Shaw *et al.* nor Cook *et al.* teach selecting a prodrug having a relative activity in the target tissue that is greater than 10 times that of the non-target tissue; wherein the target and non-target tissues are in an animal, the prodrug is administered to the animal and the relative activity is determined by analysis of the animal tissues after administration of the prodrug; wherein the target tissue is lymphoid tissue and the activity is anti-HIV activity or wherein the target tissue is liver and the activity is anti-HBV activity.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the screening method to determine the bioavailability and biostability of PMPA prodrugs as taught by Shaw *et al.* and Cook *et al.* above with the method of screening for antiviral activity of phosphonoamidate prodrugs of Glazier *et al.* because one of ordinary skill in the art would have recognized that both methods are drawn to the determination of the relative antiviral activities of phosphonoamidate prodrugs in various tissue types. One of ordinary skill in the art would have been motivated to make this combination because of the advantage demonstrated by Glazier *et al.* of being able to directly determine the specific antiviral activity of the prodrugs against specific viruses in specific target tissues in whole animals, such specificity not being determined in the method of Shaw *et al.* and Cook *et al.* which only determined the relative general antiviral activity in target tissues via bioavailability and stability assessments.

There would have been a reasonable expectation of success in making this combination because all three methods are drawn to the characterization of the levels of antiviral activity seen during the administration of phosphonoamidate prodrugs to animal tissues.

Response to Arguments

Applicant's arguments filed 06/08/09 have been fully considered but they are not persuasive.

The Applicant argues that Glazier *et al.* fails to teach or suggest the step of assaying a target tissue and a non-target tissue where the target tissue is known to be a site of viral infection and the other is not, that Glazier *et al.* do not teach comparing the infected sites with tissues not otherwise susceptible to infection by HBV, and that Glazier *et al.* were not concerned with determining if the prodrugs are more active at the sites of infection vs. sites not known to be infected (Remarks, Pg. 8, Lines 1-7).

This is not found to be persuasive for the following reasons, as discussed above, the claims only require the selection of a target tissue which is known to be a site of viral latency or infection and at least one non-target tissue.

As discussed above, one of ordinary skill in the art at the time of the invention would have known that viral infection can be tissue specific (i.e., lymphoid tissue for HIV and hepatic tissue for Hepatitis-B), therefore it would have been obvious to look at the bioavailability (hydrolysis) and stability of a prodrug which has known antiviral activity in a target tissue of interest as a means of ascertaining whether prodrug is reaching the target tissue in an active form and in what amounts. Further, one of ordinary skill in the art would have selected a non-target tissue of interest as a means of determining the potential for side effects (toxicity) in non-target tissue or the misdirection of prodrug and active drug to the wrong tissue.

Applicant's assertion of a comparison of the infected sites with tissues not otherwise susceptible to infection by HBV is not found in the instant claims and is therefore accorded no weight. Similarly, Applicant's assertion that Glazier *et al.* were not concerned with determining if the prodrugs are more active at the sites of infection vs. sites not known to be infected is not found in the instant claims (the determination if the prodrugs are more active at the sites of infection vs. sites).

The Applicant argues that Glazier *et al.* taught the administration of a dansyl phosphate prodrug to mice in a metabolism study of phosphate prodrugs and did not teach a comparison of activity in target and non-target tissues or the selection of a desired prodrug based on its relative antiviral activity (Remarks, Pg. 8, Lines 8-12).

This is not found to be persuasive for the following reasons, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a comparison of activity in target and non-target tissues) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As discussed above, one of ordinary skill in the art would have recognized the obviousness of selecting the prodrug showing the best biological stability and bioavailability in various tissues and bodily fluids because this would necessarily also provide the best *relative* antiviral activity of the prodrug in those tissues.

The Applicant argues that Shaw *et al.* chose intestine and liver because these are sites of metabolism not because they are or might be sites of infection, that Shaw *et al.* and Cook *et al.* were concerned with conducting bioavailability studies not antiviral studies while Glazier *et al.* conducted an antiviral activity study without concern about bioavailability, that indirectly measuring bioavailability by measuring antiviral activity would introduce an additional variable into the methods of Shaw *et al.* and Cook *et al.* since the preference of the viral infection would constitute an additional variable potentially masking the metabolism of the prodrug and that combination of Glazier *et al.* with Shaw *et al.* and Cook *et al.* would be anomalous because Glazier *et al.* discloses no antiviral assay using intestinal tissue (Remarks, Pg. 8, Lines 13-26 and Pg. 9, Lines 1-2.

This is not found to be persuasive for the following reasons, whatever the reasoning of Shaw *et al.* for choosing intestine and liver, that does not negate the fact that the two tissues are susceptible to specific viral infection and thus it would have been obvious to select a specific target tissue known to be a site of infection for a specific virus as well as a virally non-targeted tissue for a control. While Shaw *et al.* and Cook *et al.* conducted bioavailability studies, the determination of the biological stability and bioavailability of prodrug derived PMPA in various tissues and bodily fluids would necessarily also provide a determination of the *relative* antiviral activity of the prodrug in those tissues and fluids even if no virus were present.

Glazier *et al.* provides a direct measurement of the antiviral activity of a prodrug on active infected tissue and non-infected tissue but does not teach a screening method of a plurality of prodrugs which was why it was combined with Shaw *et al.* and Cook *et al.* The allegation that indirectly measuring bioavailability by measuring antiviral activity would introduce an additional variable into the methods of Shaw *et al.* and Cook *et al.* since the preference of the viral infection would constitute an additional variable potentially masking the metabolism of the prodrug is not persuasive as one of ordinary skill in the art would have recognized that the purpose of bioavailability and stability studies in target and non-target tissues is the determination of whether prodrug hydrolysis (metabolism) is occurring in tissues which have or are susceptible to viral infection and that hydrolysis is not or rarely occurring in tissues not having or susceptible to viral infection.

That combination of Glazier *et al.* with Shaw *et al.* and Cook *et al.* would be anomalous because Glazier *et al.* discloses no antiviral assay using intestinal tissue is not found to be persuasive because it would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the method of Shaw *et al.* to select a target tissue and non-target tissue wherein the target tissue is not small intestine because while the claimed invention excludes the use of small intestine and therefore excludes the reference as prior art for purposes of anticipation, the reference is still valid for all its teachings with regard to the obviousness of the claimed invention. Cook *et al.* teaches that it was well known at the time of the invention to screen various tissues and bodily fluids of different species for prodrug hydrolysis and that variations were known among both the site and degree of hydrolysis among species.

The Applicant argues that combination of the bioavailability studies of Shaw *et al.* and Cook *et al.* with an antiviral study of Glazier *et al.* would produce antiviral results in different tissues but that since the antiviral assays are for different viruses (each virus for an individual tissue), it would be impossible to compare relative antiviral activities (Remarks, Pg. 9, Lines 3-10).

This is not found to be persuasive for the following reasons, one of ordinary skill in the art would have been motivated to make this combination because of the advantage demonstrated by Glazier *et al.* of being able to directly determine the specific antiviral activity of the prodrugs against specific viruses in specific target tissues (lymphoid tissue for HIV and liver tissue for HBV), such specificity not being determined in the method of Shaw *et al.* and Cook *et al.* which only determined the relative general antiviral activity in target tissues. Further, no comparison step of relative antiviral activities is claimed in the instant invention.

Conclusion

No Claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL C. MARTIN whose telephone number is (571)272-3348. The examiner can normally be reached on M-F 8am-4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Martin
Examiner
Art Unit 1657

07/22/09

/Rebecca E. Prouty/
Primary Examiner,
Art Unit 1652